J. Physiol. (1945) 104, 47–51 615.783

TESTING DIPHENYLETHYLAMINE COMPOUNDS FOR ANALGESIC ACTION

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(*Received* 18 *October* 1944)

Diphenylethylamine and compounds related to it have some of the pharmacological properties of morphine: they may depress the righting reflex in rats, raise the blood-sugar level in rabbits, and produce nausea, hyperexcitability and pupil dilatation in cats (Dodds, Lawson & Williams, 1943, 1944). If the compounds are to be of clinical value they must produce analgesia. Preliminary clinical trials of four of the compounds showed that two of them (diphenylethylamine and hydroxy-diphenylethylamine) relieved the pain of patients suffering from the pressure effects of secondary deposits in malignant disease. The present paper records an attempt to estimate the analgesic potency of the compounds, but no such action could be demonstrated by the methods adopted.

TOLERANCE OF HEAT PAIN IN MAN

Method

The method of Hardy, Wolff & Goodell (1940) was used. The beam from a kilowatt lamp is concentrated for 3 sec. on a blackened area of the subject's forehead. There is a variable resistance in the circuit and the radiant energy is raised until the subject reports that the sensation of heat has changed into one of pain. The energy output of the lamp at each resistance was determined by voltmeter and ammeter readings. In view of the unsatisfactory results there was no need to calibrate the apparatus in terms of calories falling on the test area. Readings were made at 15 min. intervals.

Two subjects were each given one or two cachets by mouth, after four control readings had been made. The test was continued for 3 hr. after the cachet had been given. The subjects were ignorant of the contents of the cachets, which were either morphine hydrochloride (11 mg.), or diphenylethylamine hydrochloride (200 mg.), or lactose (200 mg.).

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Results

The mean minimum wattage at which pain was felt during the control period was calculated and the subsequent readings expressed as a percentage of this figure. The maximum increases are recorded in Table 1, which shows that neither 22 mg. of morphine hydrochloride nor 200 mg. of diphenylethylamine hydrochloride given by mouth produce any significant rise in pain threshold.

Table 1. Pain threshold measurements after taking cachets by mouth

Contents of cachet		Maximum threshold recorded as percentage of control reading: Subject 1	Subject 2
Lactose:	200 mg.	109%	107%
	400 mg.	103%	108%
Morphine HCl:	11 mg.	103%	101%
	22 mg.	102%	105%
Diphenylethylamine HCl:	200 mg.	105%	108%

American authors have used this method extensively and successfully; the failure to confirm their results is disappointing. They have usually tested morphine after parenteral administration, but successful results with non-opiate drugs given by mouth have been reported, for instance by Wolff, Hardy & Goodell (1941).

The higher dose of morphine which we used was sufficient to produce definite nausea. The subjective effects of 200 mg. of diphenylethylamine were reported independently by both subjects to resemble those of mild drunkenness.

TOLERANCE TO ELECTRIC SHOCK IN RATS

Method

The method of Sivadjian (1935) was used. A box is floored with parallel copper wires, alternate wires being connected to the positive and negative terminals of the secondary coil of a Du Bois-Reymond apparatus. A male (90–110 g.) rat is placed in the box and the distance between the primary and secondary coils of the apparatus is decreased until the rat jumps when the current is switched on. Readings are taken at 15 min. intervals. Cross-over tests have been carried out on groups of five or six rats, of which three are injected subcutaneously with the test compound, and the remainder with a similar volume of physiological saline on one day and given the reverse injections on the following day. Two control readings are made before the injection is given, and readings are continued for 1–2 hr. afterwards.

Results

Both morphine and pethidine hydrochlorides produced significant increases in pain threshold, but none of the diphenylethylamine compounds did so. In view of this failure no attempt was made to calibrate the apparatus. The

results obtained with the hydrochlorides of morphine and pethidine are graphed in Fig. 1. The graphs indicate that with the increasing dose the rise

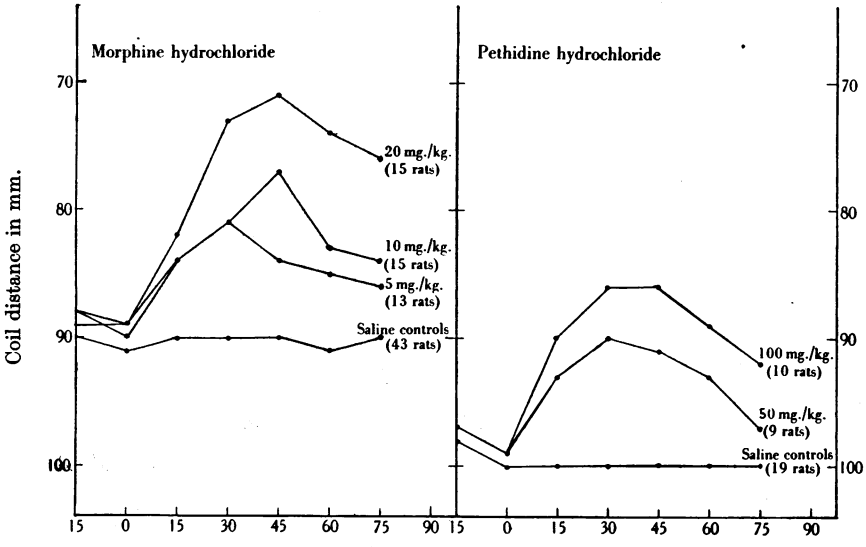

Fig. 1.

TABLE 2. Pain thresholds to electric shocks in rats

Test substance	Dose mg./kg.	No. of rats	Pre-injection reading*	Min. post-injection reading*	Max. fall
Morphine HCl	5	13 exp.†	89	81	8
		11 con.	90	89	1
	10	15 exp.	90	77	13
		15 con.	91	90	1
	20	15 exp.	89	71	18
		15 con.	90	89	1
Pethidine HCl	50	9 exp.	99	90	9
		9 con.	100	100	0
	100	10 exp.	99	86	13
		10 con.	100	99	1
β-Hydroxy-α:β-diphenyl-ethylamine HCl	50	5 exp.	85	86	—
		5 con.	83	81	2
	100	5 exp.	85	81	4
		5 con.	86	84	2
	200	10 exp.	101	96	5
		10 con.	102	101	1
	400	6 exp.	100	92	8
		5 con.	102	102	0

* Distance between coils in mm.
† exp. = experimental rats; con. = saline-control rats.

in pain threshold is increased so that the method may be capable of being adapted for quantitative assays.

In Table 2 are given the individual results with the hydrochlorides of morphine, pethidine, and β-hydroxy-α:β-diphenylethylamine. This last compound had given the most encouraging results in the clinical trials mentioned above and was therefore tested thoroughly. The drop in coil distance certainly increased with the dose, but the increases are hardly significant, certainly do not approach those attained with the other two compounds, and are suspect owing to the toxic symptoms produced with the higher doses (muscular tremor with 200 mg./kg., and convulsions in some of the rats injected with 400 mg./kg.).

The essentially negative results obtained with this compound were duplicated when the hydrochlorides of the related compounds listed in Table 3 were tested. The doses were the greatest that could be given without producing toxic symptoms. None of the compounds gave a fall in coil distance greater than has been obtained with saline controls in a group of the same number of rats.

TABLE 3. List of compounds tested with negative results

Compound*	Dose (mg./kg.)
αβ-Di(*p*-anisyl)ethylamine (M1)	100
αβ-Diphenyl-ethylene-diamine (M2)	500
αβ-Diphenylethylamine (M3)	100
β-Hydroxy-αβ-diphenyl-*n*-propylamine (M5)	100
β-Hydroxy-αβ-diphenyl-*n*-butylamine (M6)	100
Dimethylamino-benzyl-phenyl-ketone (M7)	50
β-Hydroxy-αβ-diphenyl-*n*-propyl dimethylamine (M8)	100
β-Hydroxy-αβ-diphenyl-*n*-butyl dimethylamine (M9)	100
α-(*p*-Hydroxyphenyl)-β-phenyl-ethylamine (M15)	50
α-Phenyl-β-*cyclo*-hexyl-ethylamine (M16)	50
	100
α-(*p*-Anisyl)-β-*cyclo*-hexyl-ethylamine (M17)	50
	100
α-*cyclo*-Hexyl-β-phenyl-ethylamine (M18)	50

* Each compound was tested as hydrochloride, and the laboratory numbers in brackets correspond to those in Dodds *et al.* (1944).

DISCUSSION

This failure to demonstrate analgesic activity in the diphenylethylamine compounds only applies to one form of painful stimulus, but the fact that pethidine gives satisfactory results does not suggest that the method of testing is at fault. Clinical trials by other workers not yet reported have confirmed our own observation that β-hydroxy-α:β-diphenylethylamine (M4) will relieve the particular pain associated with pressure on nerve caused by malignant growths, but have demonstrated little or no analgesic action on other more generalized types of pain. The reason for this apparently exclusive type of analgesic action may be related to an inhibition of nerve conduction and is being investigated.

SUMMARY

1. No significant rise in the pain threshold to heat in man was produced when 22 mg. of morphine hydrochloride or 200 mg. of diphenylethylamine were given by mouth. The latter administration produced subjective symptoms of mild drunkenness.

2. A method of measuring the pain threshold to electric stimuli in rats is described. Significant rises in threshold were produced by the hydrochlorides of morphine (5–20 mg./kg.) and pethidine (50–100 mg./kg.), but not by the hydrochlorides of diphenylethylamine and related compounds.

We are grateful to I. A. Hepple for technical assistance, and to Boots Pure Drug Co. for a supply of α-hydroxy-α:β-diphenylethylamine.

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Note added in proof (30 *Jan.* 1945). Subsequent tests have shown that mild analgesics (aspirin and antipyretic compounds of the phenetidine series) do not affect the tolerance of rats to electric shocks as determined by the method used above.